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*Publication date:*  
2012

*Document Version*  
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

*Citation (APA):*  
Stockmarr, A. (Author), Bødker, R. (Author), & Nielsen, L. (Author). (2012). Detection of Dairy Herds at risk for changing Salmonella Dublin status. Sound/Visual production (digital) <http://www.statistiksymposium.dk/>

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# Detection of Dairy Herds at risk for changing *Salmonella* Dublin status



Symposium in Applied Statistics 2012

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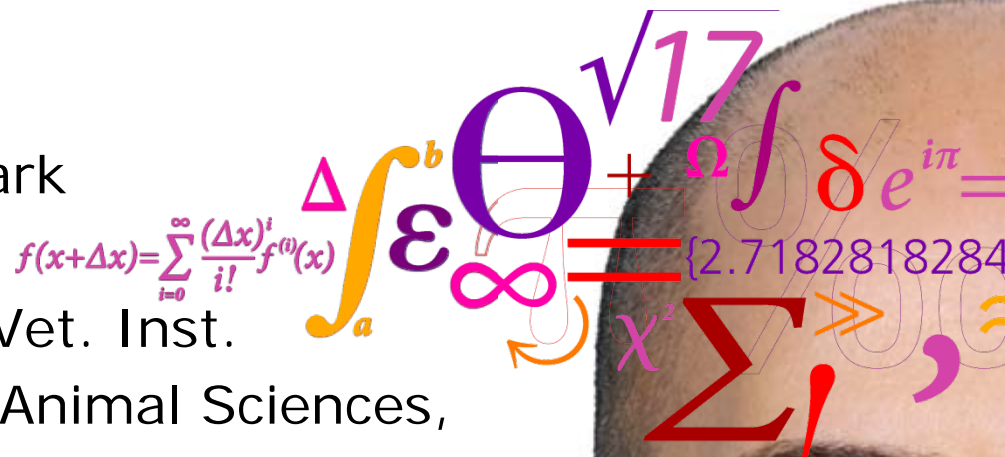
**Rene Bødker**, DTU National Vet. Inst.

**Liza Nielsen**, Dept. of Large Animal Sciences,  
Univ. of Copenhagen

DTU Informatics

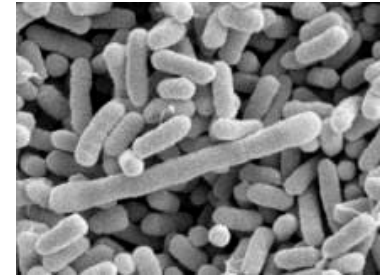
Department of Informatics and Mathematical Modeling

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# Background

- *Salmonella* Dublin (S. Dublin) is a specific serotype of the *Salmonella* bacterium
- S. Dublin is host-adapted to cattle, and the most prevalent serotype found in cattle in Denmark (~60-70% of all isolates)
- S. Dublin is a rare but serious zoonosis that causes severe disease and deaths in humans every year (10-40 hospitalized cases per year in Denmark).



# S. Dublin Symptoms

- Unthrifty calves
- Fever
- Diarrhoea (bloody)
- Pneumonia
- Death
- Abortions



# *The Salmonella* Dublin surveillance and eradication programme in Denmark

- Eradication campaign until 2014
- Goal: *The Danish cattle population free from Salmonella Dublin in 2014*
- 2010-2012: Sanctions to improve motivation
- 2013-2014: Veterinary Authorities will handle infected herds through law enforcement



# *The Salmonella* Dublin surveillance and eradication programme in Denmark



- Surveillance program since 2002:
- Cattle herds are classified as follows, based on Bulk Tank Milk/blood sample antibodies and trade contacts:

Level 1: Most likely **free** from salmonella

Level 2: **Too high antibody** levels or contact to other herds in Level 2 or 3

Level 3: **Clinical** *Salmonella* Dublin diagnosis and culture positive

Unknown: Only non-dairy herds with too **few samples** to classify (hobby herds)

# *The Salmonella* Dublin surveillance and eradication programme in Denmark



- Surveillance program since 2002:
- Cattle herds are classified as follows, based on Bulk Tank Milk/Blood sample antibodies and trade contacts:

**Level 1:** Most likely **free** from salmonella

**Level 2:** **Too high antibody** levels or contact to other herds in Level 2

For the present work we do not distinguish between level 2 and 3

# Reasons for assigning Level 1 to dairy herds

**Salmonella Dublin Level 1** is given if:

1. Valid bulk tank milk antibody **measurements exists** – and
2. The last 4 bulk tank milk antibody measurements, gathered with at least 3 weeks in between, shows an **average ODC-value of less than 25** – and
3. The latest Salmonella Dublin measurement has **not shown an increase of more than 20**, compared to the average of the three preceding measurements - and
4. A number of circumstances mainly related to trade and missing data do not hold.

**Otherwise, Salmonella Dublin Level 2 is given.**



# Bulk Tank Milk antibody measurements from dairy herds



- Collected routinely every three months.
- Thus, a very long period for an infection to develop before a dairy herd is possibly re-classified.
- Sanctions and law enforcement gives farmers an incentive to act if they suspect an infection is present.
- There is therefore a need to identify herds at risk of changing S. Dublin level, based on information a quarter earlier than re-classification takes place.

# Risk Herds

- Are herds 'at risk of' changing level from 1 to 2; we will start out with this loose definition.
- Risk herds are thus Level 1 ("Status 1") herds.

## **Purpose of current study:**

- To determine appropriate definitions for a risk herd, based on available factors one quarter prior to a possible level shift.

# The probability of changing S. Dublin status

If  $X_{i,t}$  denotes the BTM measurement for herd  $i$  at time  $t$ , and  $M_{i,t}$  the mean of the last 3 measurements,  $M_{i,t} = \frac{1}{3} \sum_{j=1}^3 X_{i,t-j}$  then the probability  $p_{i,t}$  of a status change is given as

$$p_{i,t} = P\left(\frac{1}{4} X_{i,t} + \frac{3}{4} \left(\frac{1}{3} \sum_{i=1}^3 X_{i,t-i}\right) > 25 \vee X_{i,t} - \left(\frac{1}{3} \sum_{j=1}^3 X_{i,t-j}\right) > 20 \mid X_{i,t-1}, X_{i,t-2}, X_{i,t-3}\right)$$

ie.

$$p_{i,t} = P\left(\frac{1}{4} X_{i,t} + \frac{3}{4} M_{i,t} > 25 \vee X_{i,t} - M_{i,t} > 20 \mid M_{i,t}\right)$$

$p_{i,t}$  is modeled through a logistic regression:

$$\log it(p_{i,t}) = \sum \beta_k Z_{i,k,t}$$

through successive conditioning on the BTM measurements.

# What makes herds become Risk Herds?

- bulk tank milk measurements, trade, neighbors and herd size

- Bulk tank milk measurements:
  - High antibody levels;
  - Unstable development in measurements.
- Trade:
  - That animals are bought from herds that turn out to be Status 2 herds;
  - that many animals are bought;
  - that many herds are traded with.
- Neighbors:
  - That many neighbors are assigned Status 2;
  - That there are many neighbors.
- Size:
  - That the herd is large.

## Available Data

- Quarterly bulk tank milk measurements 2002-2008 for 9397 dairy herds;
- Geographical coordinates for dairy and non-dairy cattle herds and their quarterly S. Dublin level;
- All performed trades at animal level 2002-2008;
- Data on herd sizes; Only 2004-2008 er usable.

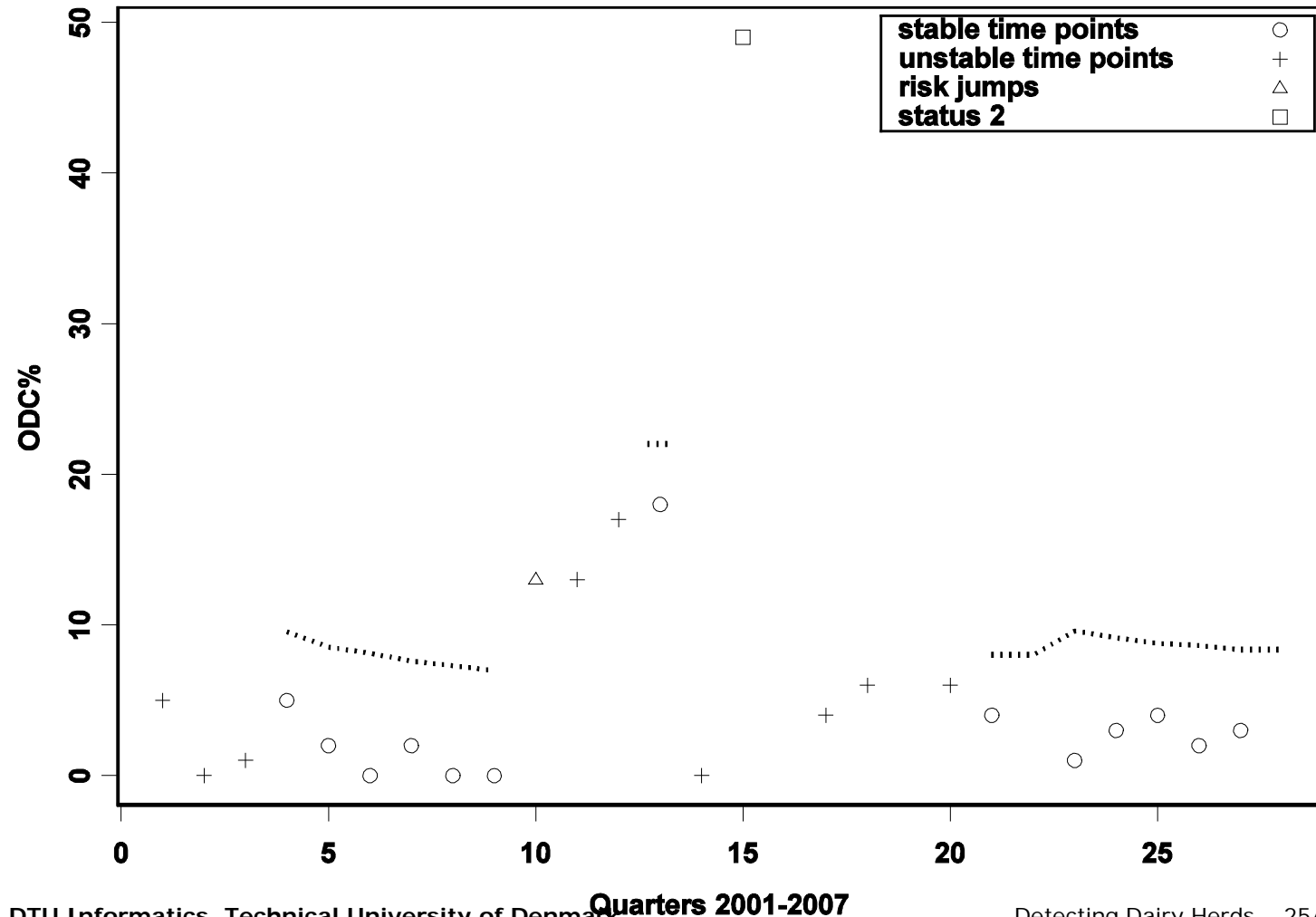
# BTM measurements and Alarm Herds

- BTM measurement enter covariates through  $M_{i,t}$ ; obviously a high level of recent antibody levels will increase the risk of a Status 2 change.
- But also sudden (upwards) deviations from a stationary development could indicate an emerging infection. BTM measurements also enters through *Alarm Herd* status:
- Alarm Herd concept: A Status 1 herd A is an Alarm Herd at a timepoint  $t_0$ , if BTM measurements for A for at least the previous 4 time points do not vary more than a standard 95% confidence interval would predict, and the BTM measurement for A at time  $t_0$  is **above** this level, and above an upward threshold  $c > 0$ .

# Alarm Herds

- Alarm Herds are Level 1 herds: The jump from the steady progression should be big (to a level  $> c$ ), but not so big that it triggers a Status 2 classification.
- Time points where BTM measurements for A for at least the previous 4 time points do not vary more than a standard 95% confidence interval would predict are called stable timepoints.
- When a herd leaves a stable state to become unstable, we say that a jump has occurred.
- When a herd becomes an Alarm Herd, we say that a risk jump has occurred.

# A BTM measurement progression example





# Estimation of $c$

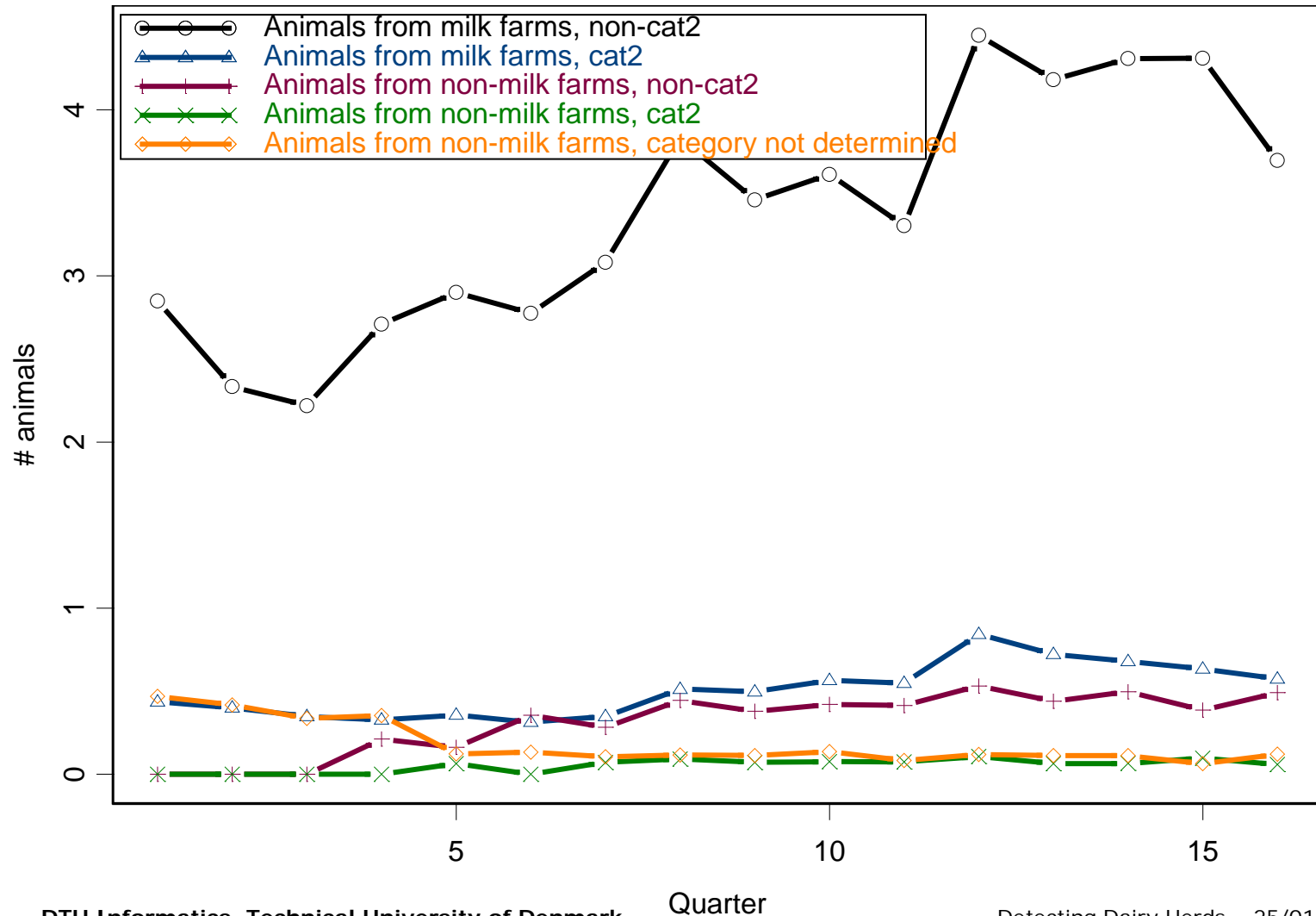
- We included Alarm Herd status in the basic logistic regression model with varying values of  $c$  (integer ODC values), to gain a series of competing models;
- We chose the model with the optimal Akaike Information;
- Consequently, we estimated  $c$  to be 13.

# Trade information



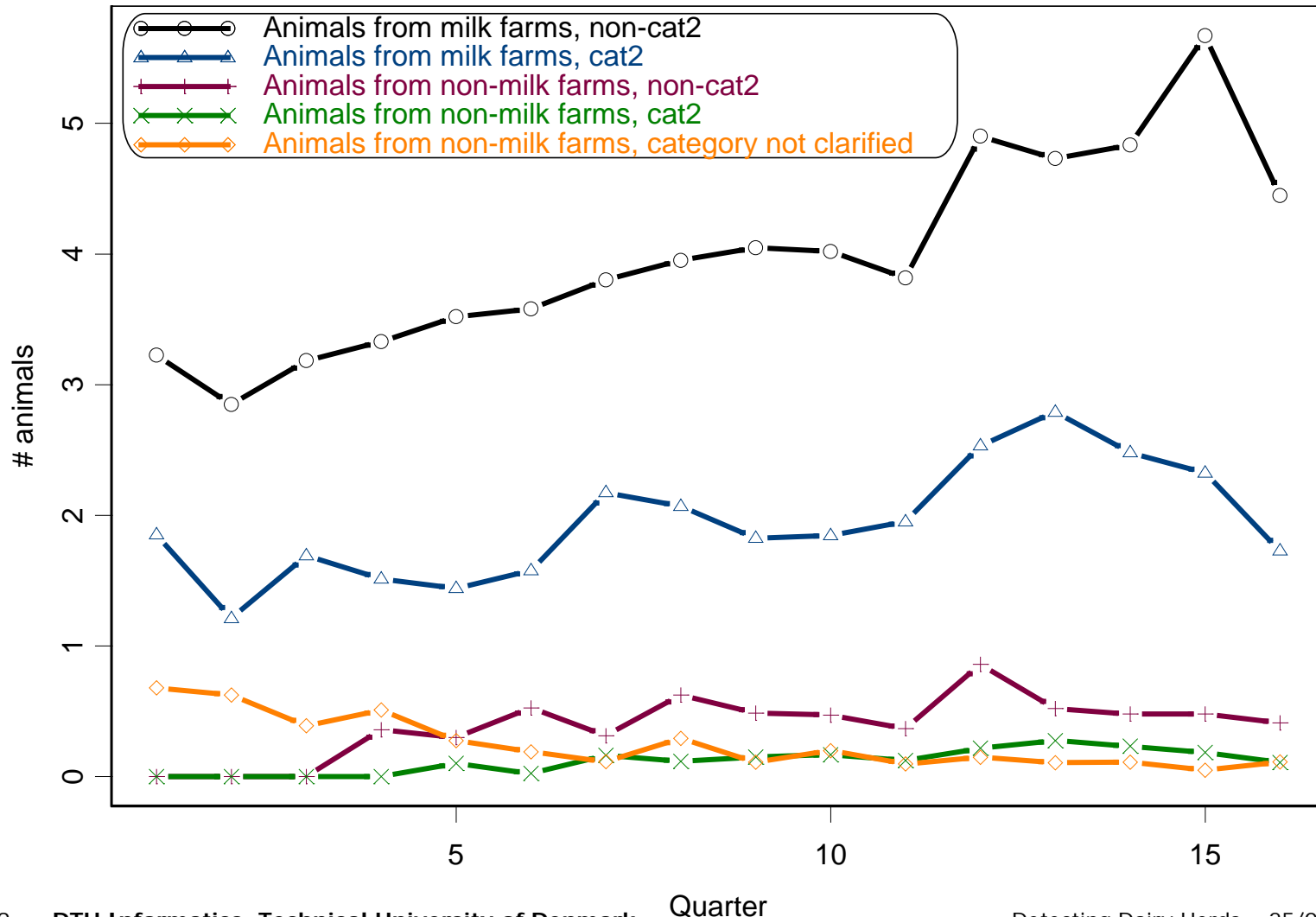
# Trade

## Milk producing non-cat 2 herds purchases 2004-2007



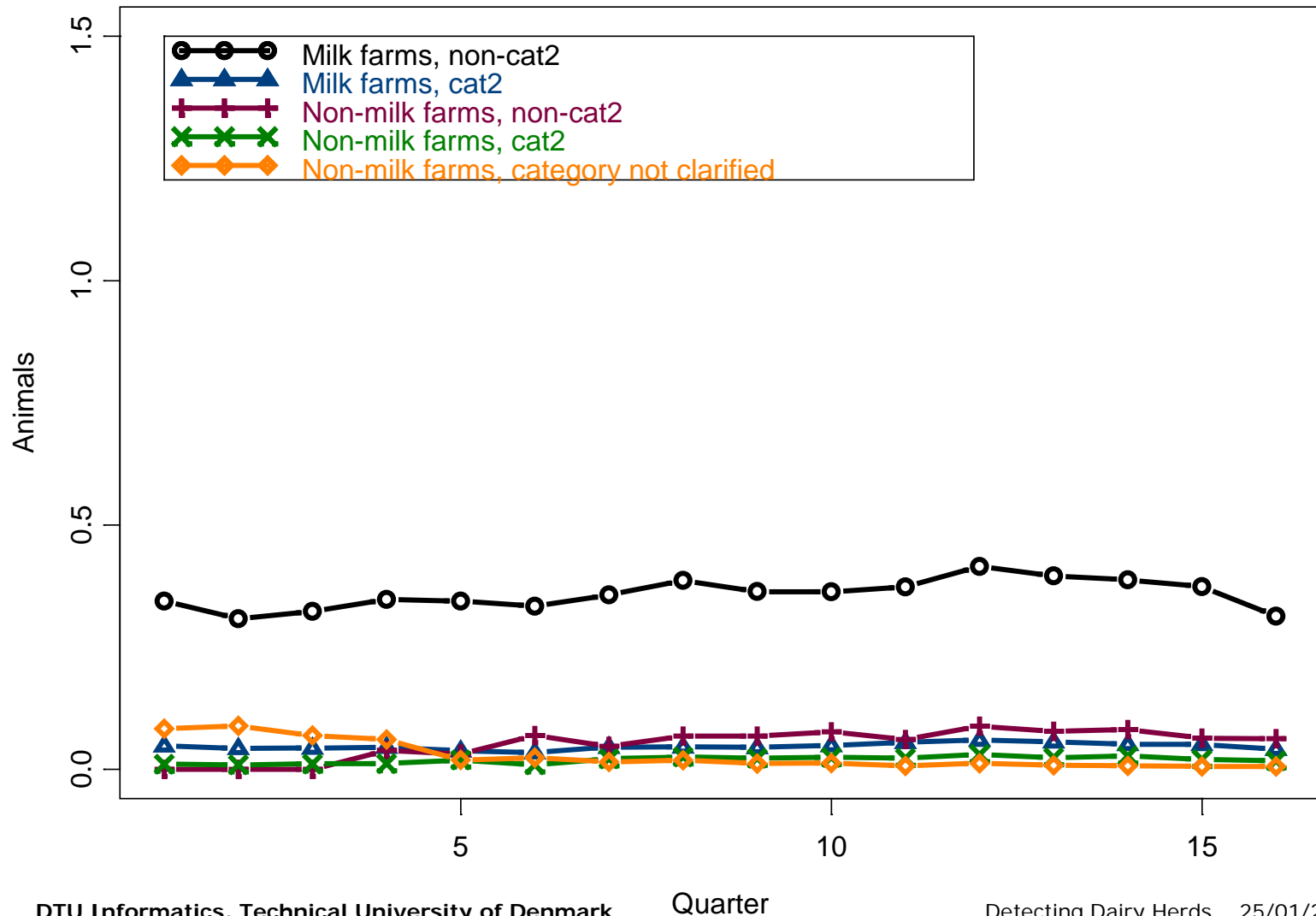
# Trade II

## Milk producing cat 2 herds purchases 2004-2007



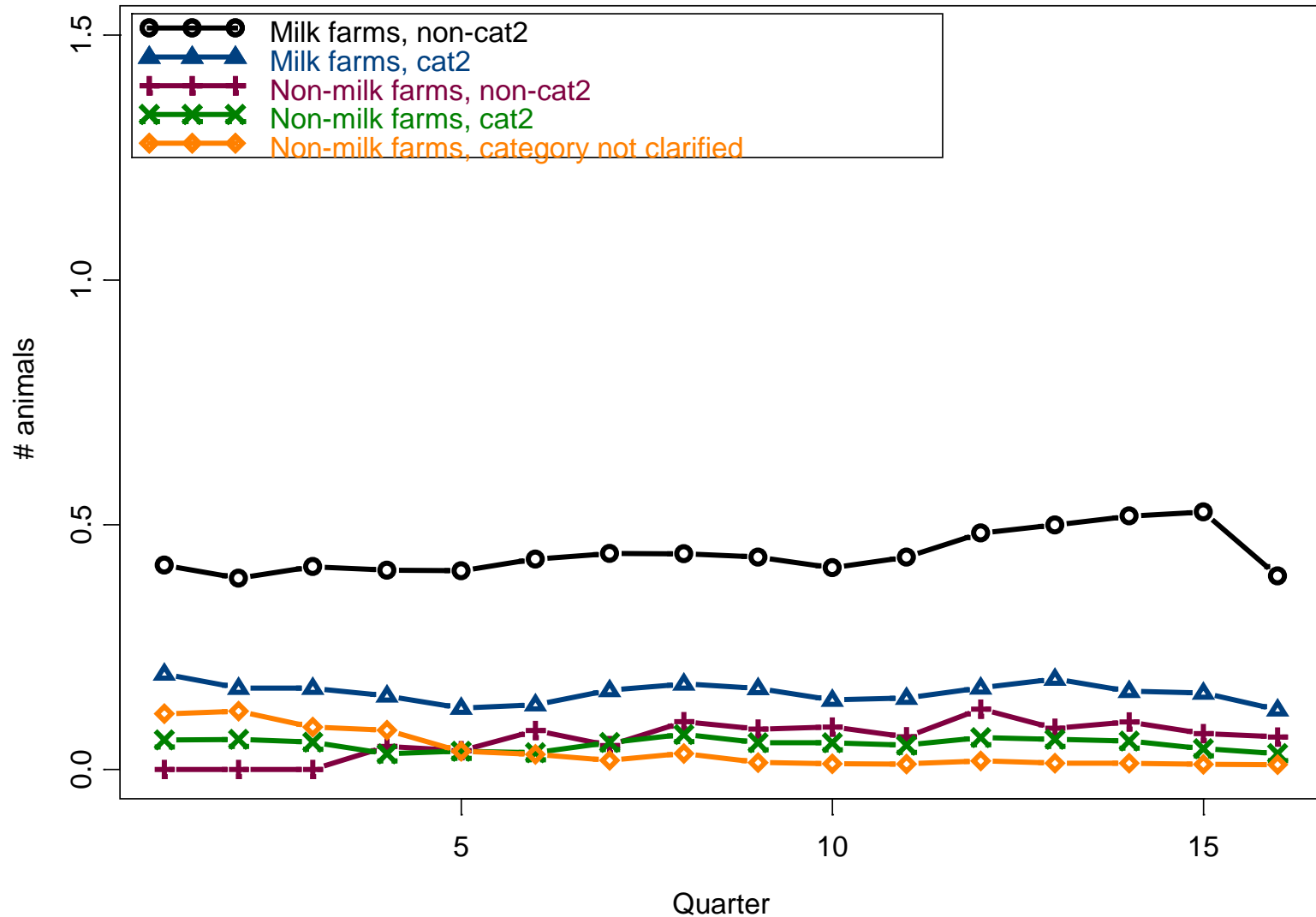
# Trade III

Trade partners for milk producing non-cat 2 farms 2004-2007

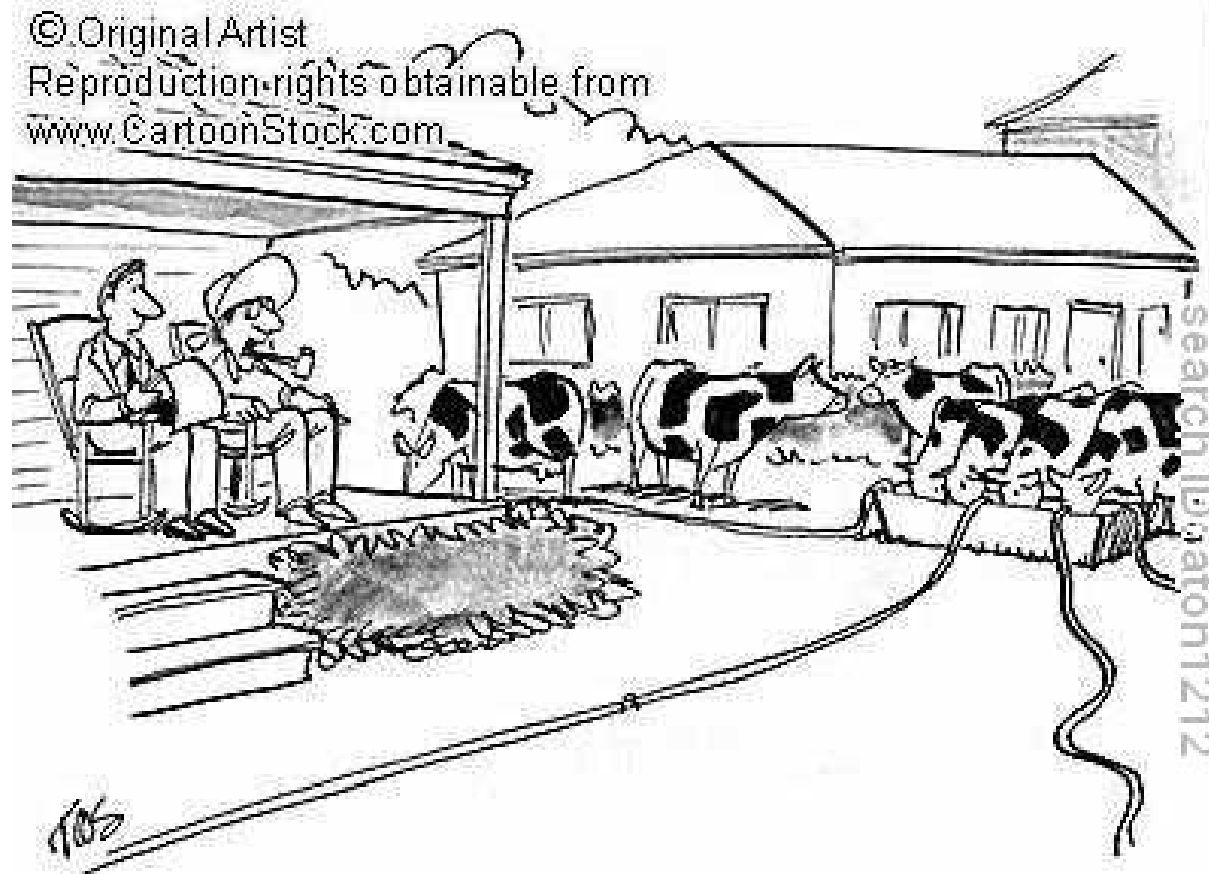


# Trade IV

Trade partners for milk producing cat2 farms 2004-2007



# Neighbor herds and animals



**"I used to have a real nice lawn  
before the cows moved in next door."**

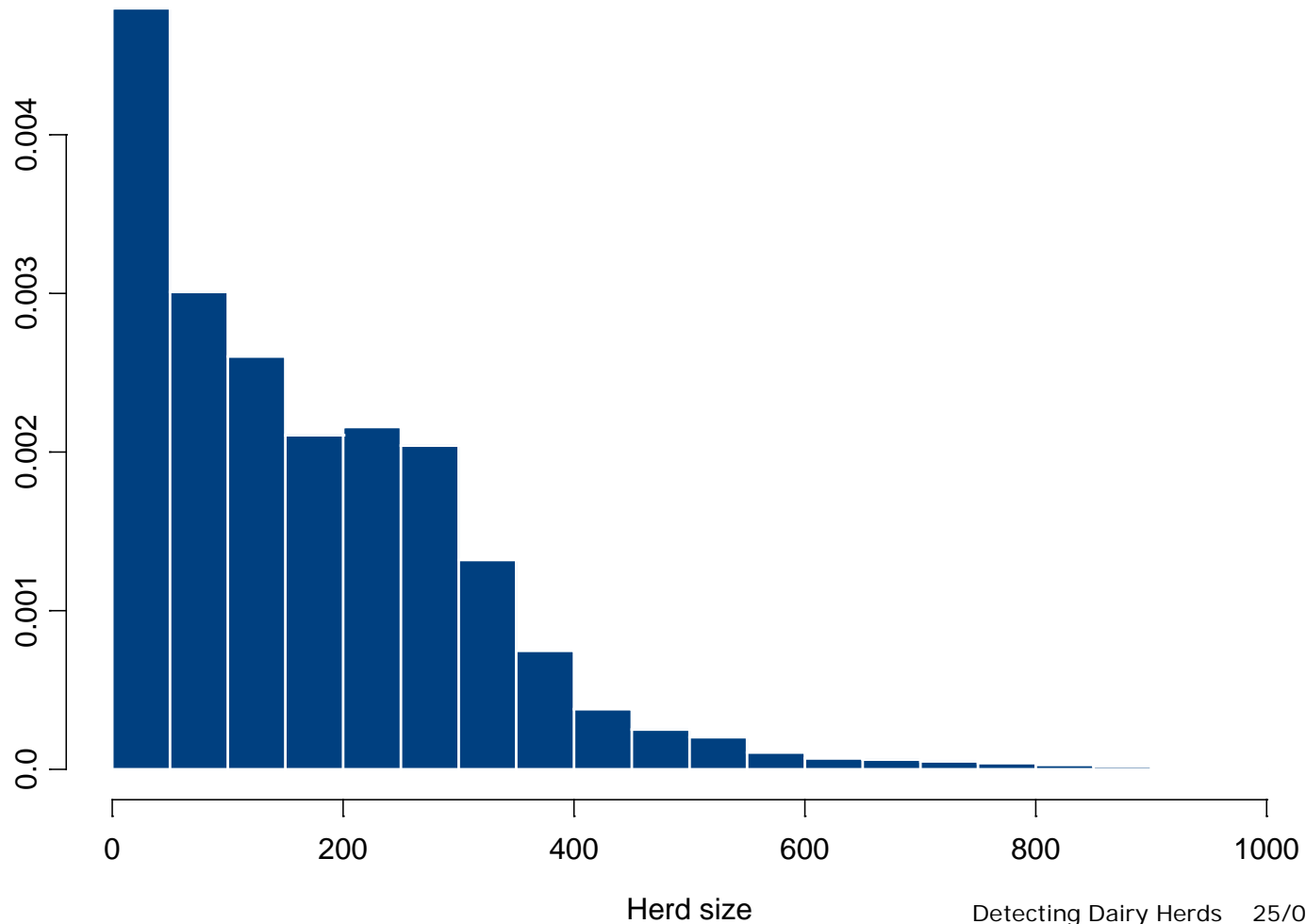
# Neighbors – What is a neighbor?

- Ersbøll & Nielsen (2008): 4.9 km is the average 'range of influence' for local spread of Salmonella.
- We define Neighbors to be herds with a distance of less than 4.9 km from the herd in question.
- Counted for all dairy herds in Denmark, dynamically (ie., a time series).
- We consider both the number of herds and the number of animals within this radius.
- The neighbor effect is a hidden geographical component, in that clusters of herds will have many Neighbors (well known places in Jutland).



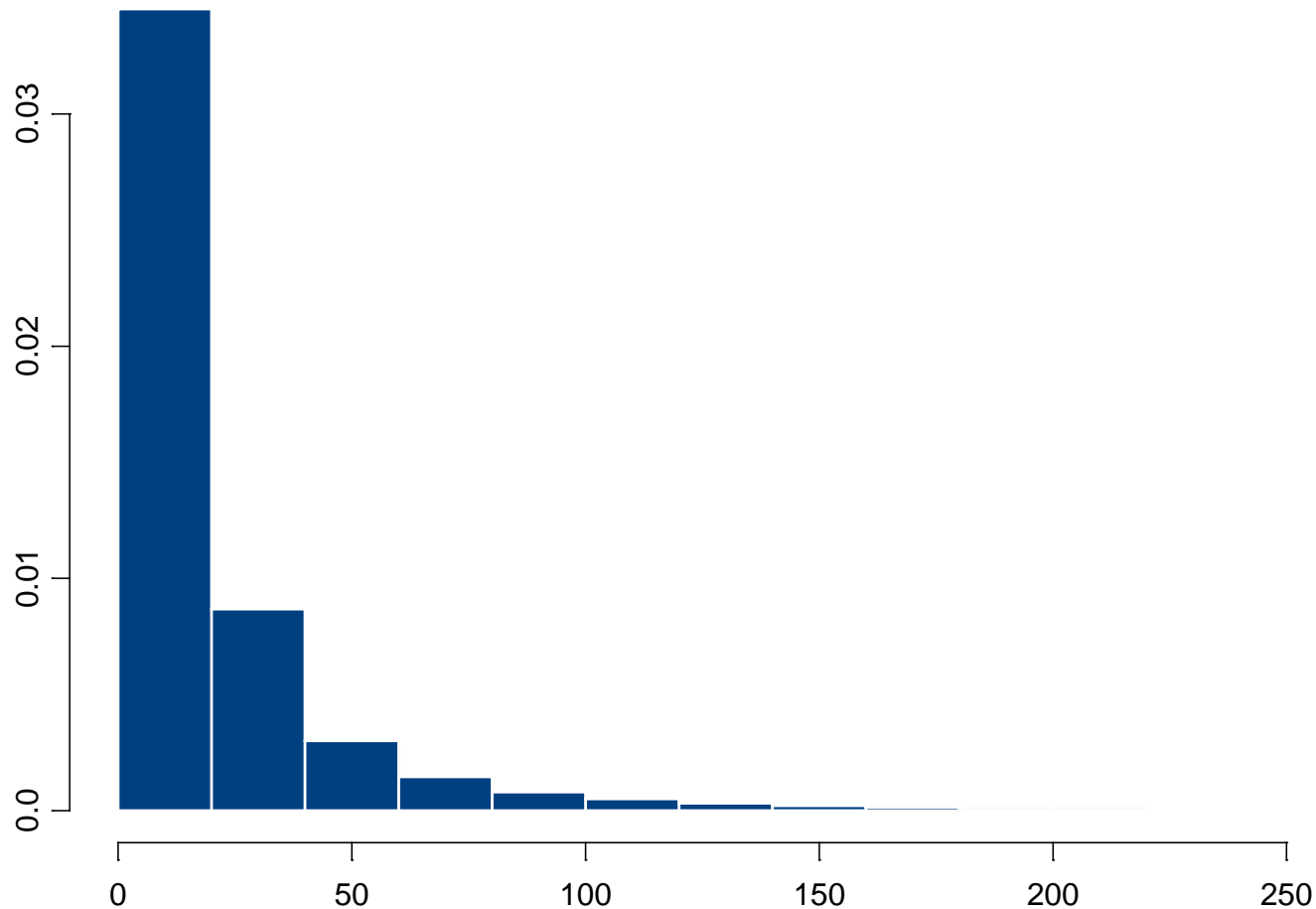
# Herd Sizes, dairy herds

Histogram, milk producing herds

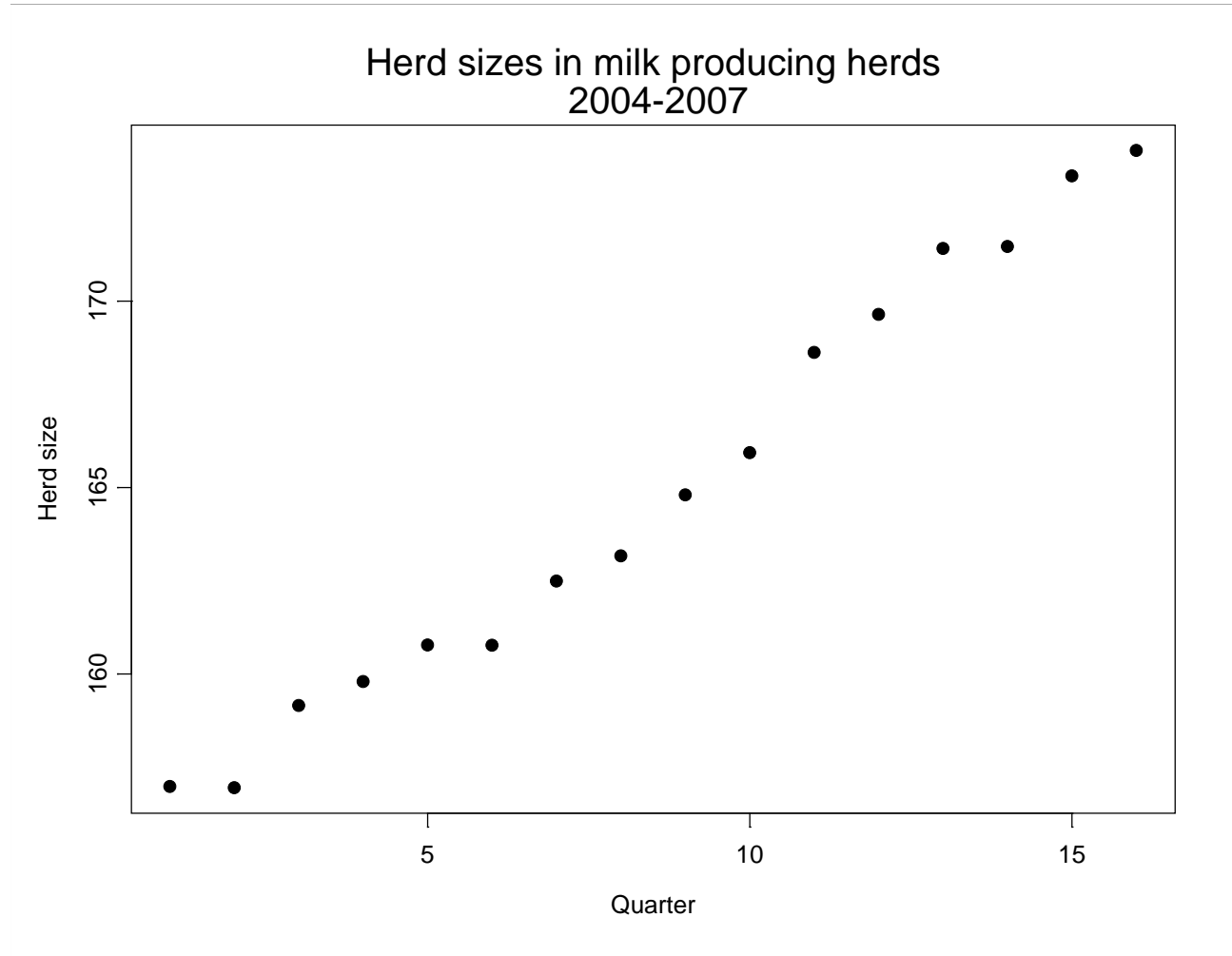


# Herd sizes, non-dairy herds (used as neighbors only)

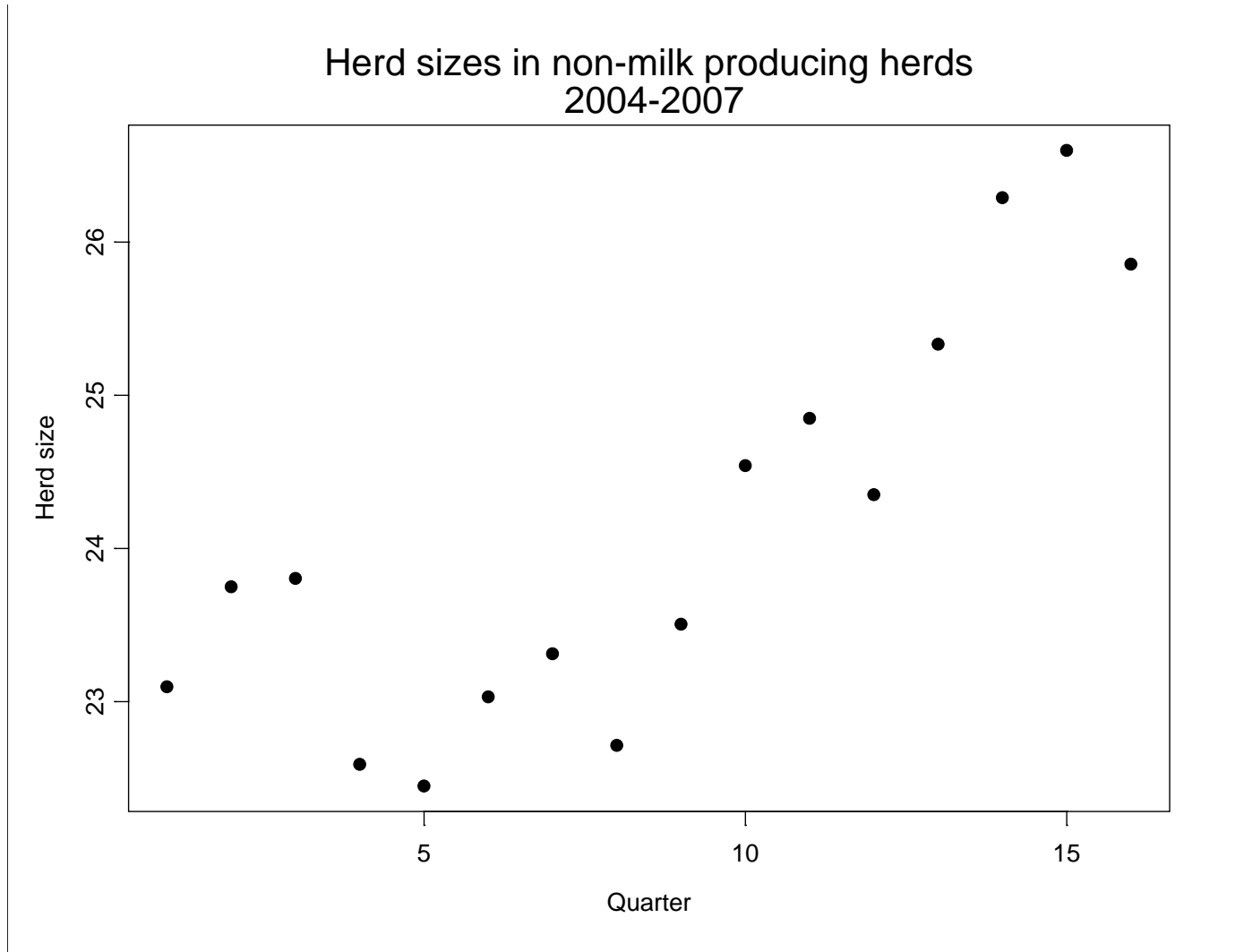
Histogram, milk producing herds



# Dynamic herd sizes, dairy herds



# Dynamic herd sizes, non-dairy herds



| Explanatory variable  | Type of effect  | Mean of explanatory variable | Regression coefficient $\pm$ S.E. | P       |
|---|-----------------|------------------------------|-----------------------------------|---------|
| Intercept   | Main effect     | 1                            | 4.90 $\pm$ 0.20                   | <0.0001 |
| Season , 1 <sup>st</sup> quarter  | Seasonal effect | 0.27                         | -6.80 $\pm$ 0.30                  | <0.0001 |
| Season , 2 <sup>nd</sup> quarter  | Seasonal effect | 0.26                         | -7.14 $\pm$ 0.32                  | <0.0001 |
| Season , 3 <sup>rd</sup> quarter  | Seasonal effect | 0.26                         | -6.62 $\pm$ 0.29                  | <0.0001 |
| Mean of last 3 (Mean3)  | Main effect     | 5.34                         | 0.12 $\pm$ 0.016                  | <0.0001 |
| Mean3, 1 <sup>st</sup> quarter**  | Interaction     | 5.25*                        | 0.071 $\pm$ 0.021                 | <0.0001 |
| Mean3, 2 <sup>nd</sup> quarter  | Interaction     | 5.27*                        | 0.11 $\pm$ 0.022                  | <0.0001 |
| Mean 3, 3 <sup>rd</sup> quarter   | Interaction     | 5.47*                        | 0.067 $\pm$ 0.021                 | <0.0001 |
| Trade contacts with Status 2 herds  | Main effect     | 0.037                        | 0.44 $\pm$ 0.21                   | -       |
| Animals traded with Status 1 herds  | Main effect     | 2.62                         | 5.30e-3 $\pm$ 3.44e-3             | -       |
| Animals traded with Status 2 herds  | Main effect     | 0.29                         | 0.033 $\pm$ 0.010                 | -       |
| Neighbour Status 2 dairy herds  | Main effect     | 4.28                         | 0.066 $\pm$ 0.033                 | -       |
| Neighbour animals from Status 2 dairy herds   | Main effect     | 816                          | 4.01e-4 $\pm$ 1.61e-4             | -       |
| Alarm1  | Main effect     | 0.019                        | 0.58 $\pm$ 0.32                   | 0.001   |
| Mean3 $\times$ Animals traded with Status 2 herds                                   | Interaction     | 2.51                         | -1.14e-3 $\pm$ 6.41e-4            | <0.0001 |
| Mean 3 $\times$ Neighbour animals from Status 2 dairy herds                         | Interaction     | 5370                         | -1.27e-5 $\pm$ 5.70e-6            | <0.0001 |
| Trade contacts with Status 2 herds $\times$ Animals traded with Status 2 herds      | Interaction     | 0.40                         | -9.33 e-3 $\pm$ 6.21e-3           | <0.0001 |
| Neighbour Status 2 dairy herds $\times$ Neighbour animals from Status 2 dairy herds | Interaction     | 8250                         | -1.69e-5 $\pm$ 0.73e-6            | <0.0001 |

- No effect of trade two quarters back.
- Interaction across groups of covariates with  $M_t$  only.
- Alarm Herd status (one quarter back) has a large impact;
- Effect of animals (traded and neighbors) decreases when level of  $M_t$  increases; those with a high level of  $M_t$  have a risk independent of animals purchased and animals traded.
- Independent of  $M_t$ :  
**Trade contacts with Status 2 herds and Alarm Herd status.**

# Remarks II

- **Trade with Status 1 herds** has an effect through the number of purchased animals, while **trade with Status 2 herds** has an effect both through the number of trade partners and the number of purchased animals.
- Status 1 trade contacts is not significant.
- Neighbors has an effect through **Status 2 dairy neighbor farms** and **Status 2 dairy animals**.
- Non-dairy neighbours and Status 1 dairy neighbors are not significant.

# Model based on 2007 data only

**Table 2 Explanatory variables, regression coefficients and P-values in the final logistic regression model for a change in herd classification from Status 1 to Status 2 in the Danish surveillance programme for S. Dublin in dairy herds, base on data from 2007**

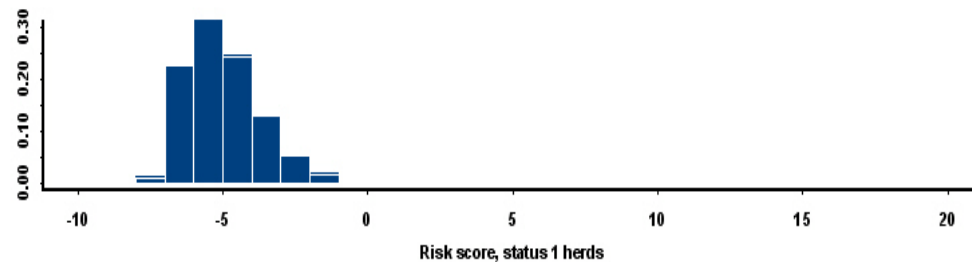
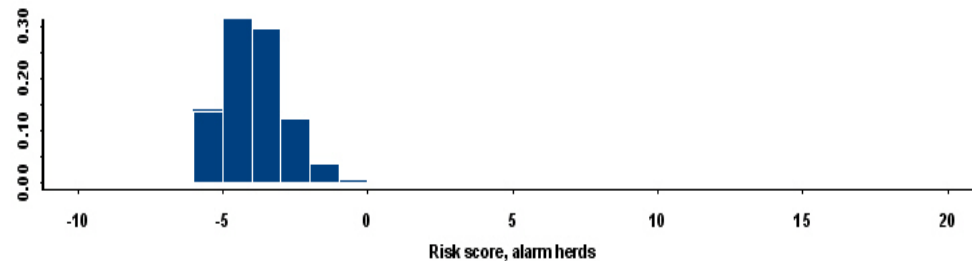
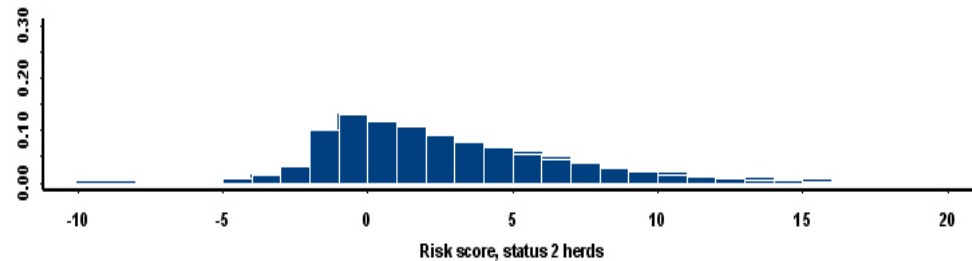
| Explanatory variable                                   | Type of effect | Mean of explanatory variable | Regression coefficient $\pm$ S.E. | p       |
|--|----------------|------------------------------|-----------------------------------|---------|
| Intercept  | Main effect    | 1                            | -7.05 $\pm$ 0.39                  | <0.0001 |
| Mean3  | Main effect    | 6.50                         | 0.22 $\pm$ 0.02                   | <0.0001 |
| Trade contacts with Status 2 herds                     | Main effect    | 0.048                        | 0.70 $\pm$ 0.37                   | 0.0006  |
| Number of animals in neighbouring Status 2 dairy herds | Main effect    | 758                          | 0.0179 $\pm$ 0.0113               | 0.003   |
| Alarm1   | Main effect    | 0.023                        | 1.08 $\pm$ 0.69                   | 0.006   |



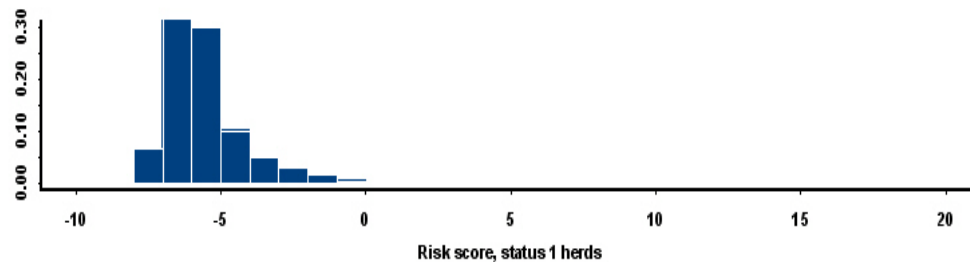
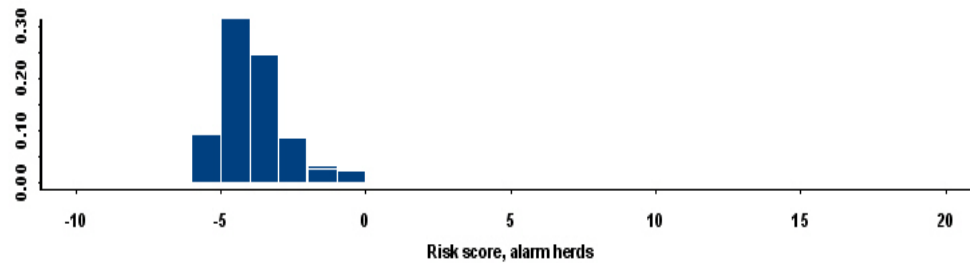
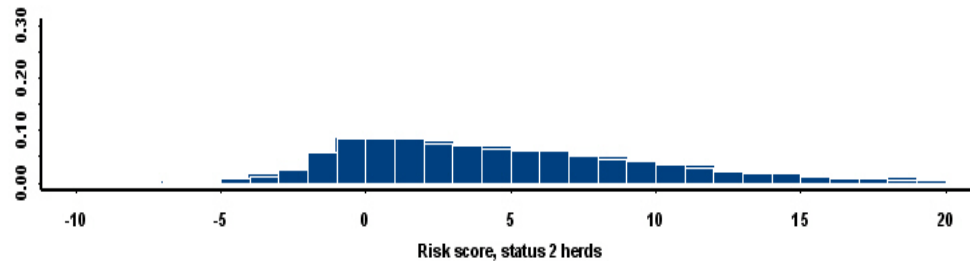
# Risk Scores

- We used the linear predictor as a risk score index.
- Which index value is high enough to consider a given herd to be a 'risk herd', where the farmer should intervene if possible?

# Risk Scores – big model

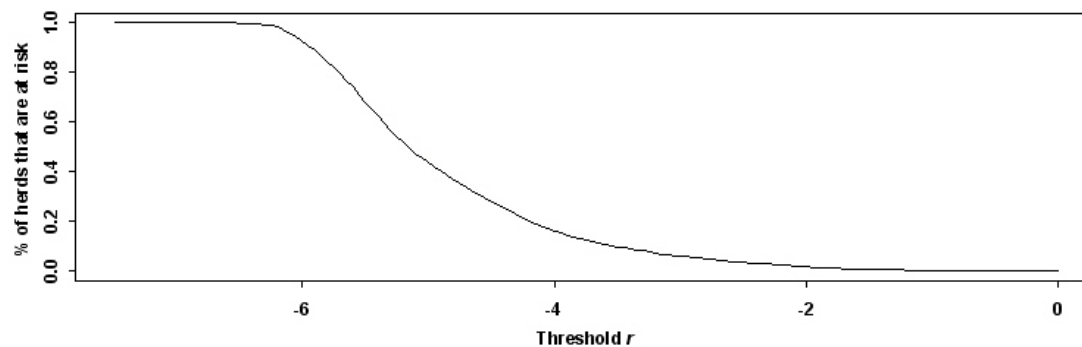
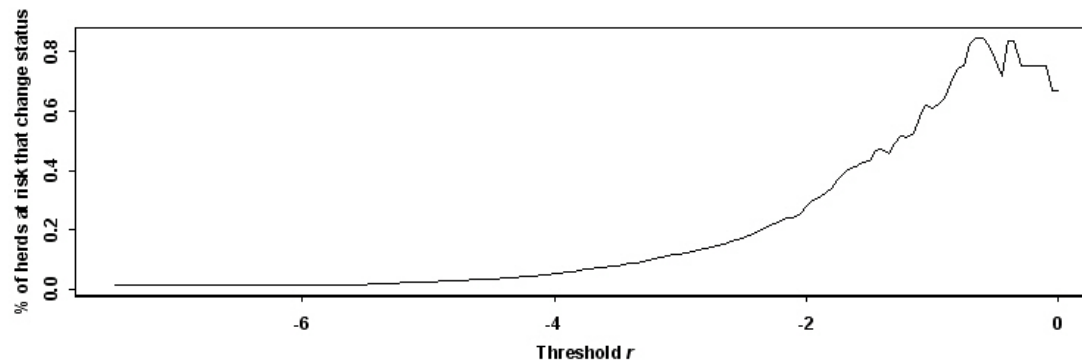


# Risk Scores – small model



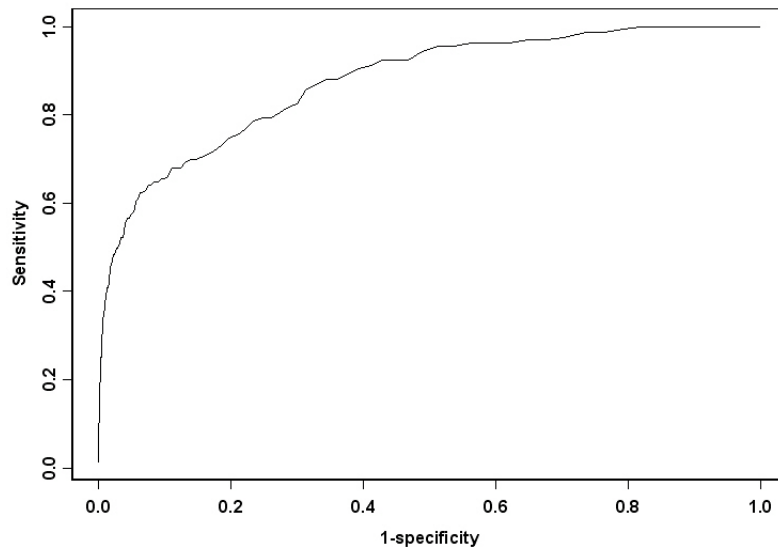
# Definitions of risk herds

- A threshold  $r$  that defines a herd to be a risk herd if the risk score is  $> r$  represents a trade-off between number of herds at risk and the frequency with which they change status:

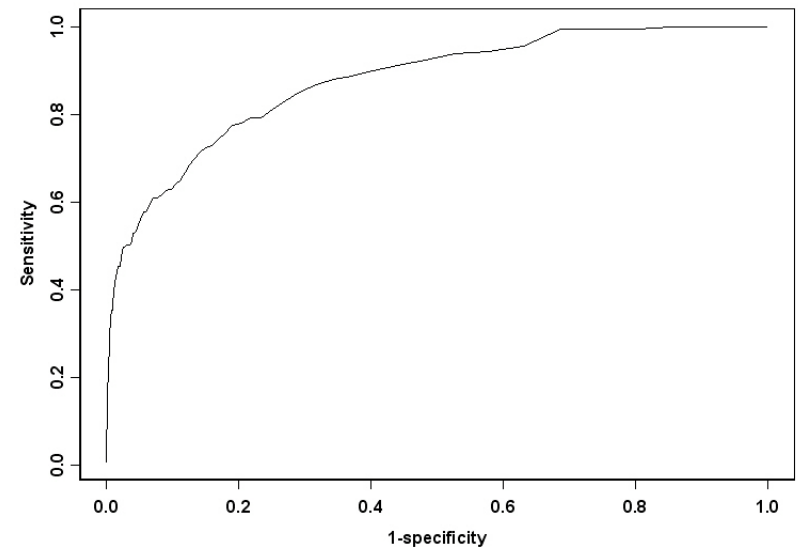


# Predictive power

Coefficients re-estimated based on 2004-2006 data, and used to predict 2007 data: ROC curves when threshold varies



Big model



Small model

# Small model versus big model

- Tempting to choose the simpler model;
- Predictive power is similar and model is much less complicated;
- However, the model could not be reproduced in full when applied to different cohorts of the data; we have no explanation for this.
- We recommend use of the big model.

- Threshold is optimized based on predictive power of the big model as

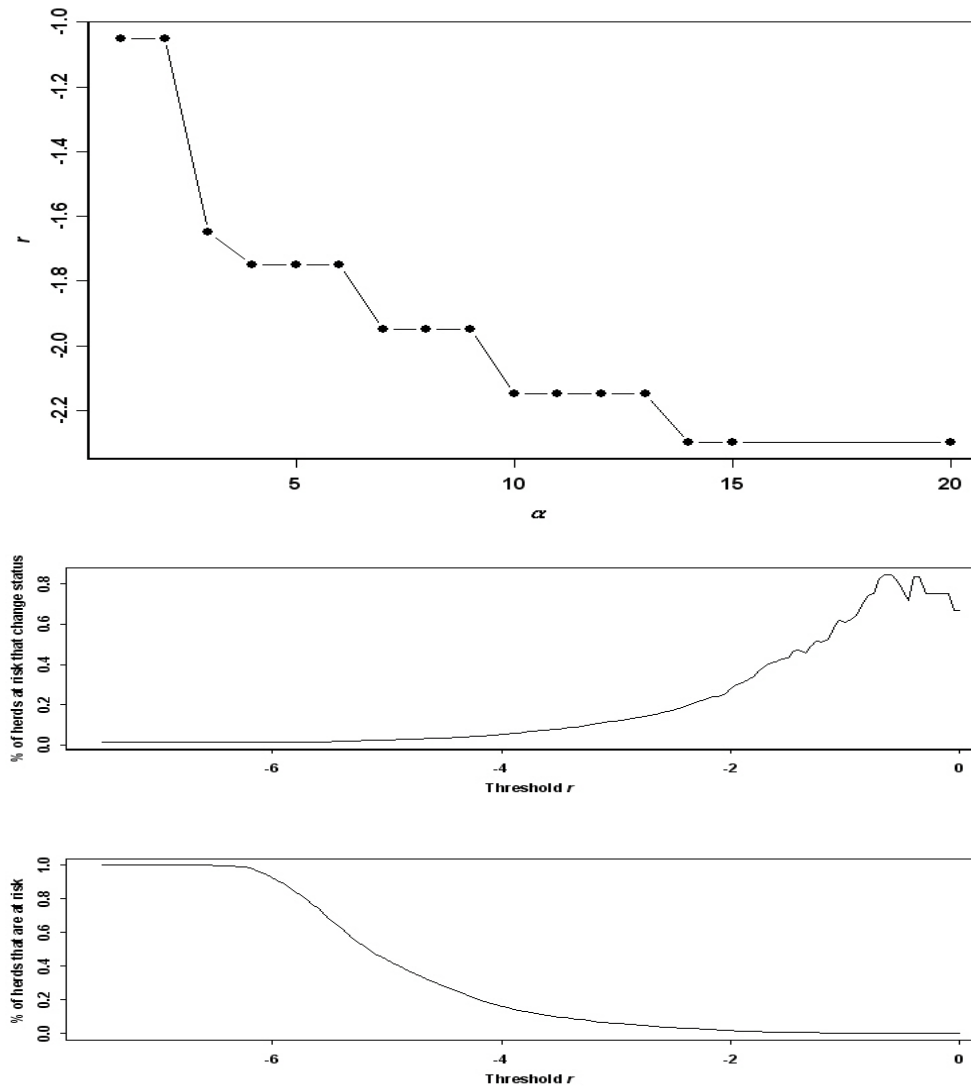
$$r = -1.05$$

- However, it is much more important to predict those that change status than those that do not.
- Let  $\alpha$  denote the importance of predicting a status change correctly relative to a non-change, and let **C** be the event “change of status”, and **PC** the event that a herd is classified as a Risk Herd. Instead of optimizing average predictability, we optimise the importance function

$$\alpha P(C|PC)P(PC) + P(C^{\neg}|PC^{\neg})P(PC^{\neg})$$

where “ $\neg$ ” signifies negation.

# Threshold value as a function of importance





# Suggested estimation of $\alpha$ based on farmer incentive

- Loss if a Status 2 herd is not correctly predicted:

$$\begin{aligned} & \text{Price}[3 \text{ months in Status } 2] \\ & - \text{Price}[3 \text{ months in Status } 2] * \\ & \quad \text{P(Interventions fail)} \\ & - \text{Price[Interventions]} \end{aligned}$$

- Loss if a Status 1 herd is not correctly predicted:

$$\text{Price[Interventions]}$$

$$\hat{\alpha} = \frac{\text{Price}[3 \text{ months in Status } 2] * \text{P(Interventions succeed)}}{\text{Price[Interventions]}} - 1$$

# Suggested estimation of $\alpha$ based on societal costs

Replace `Price[3 months in Status 2]` by

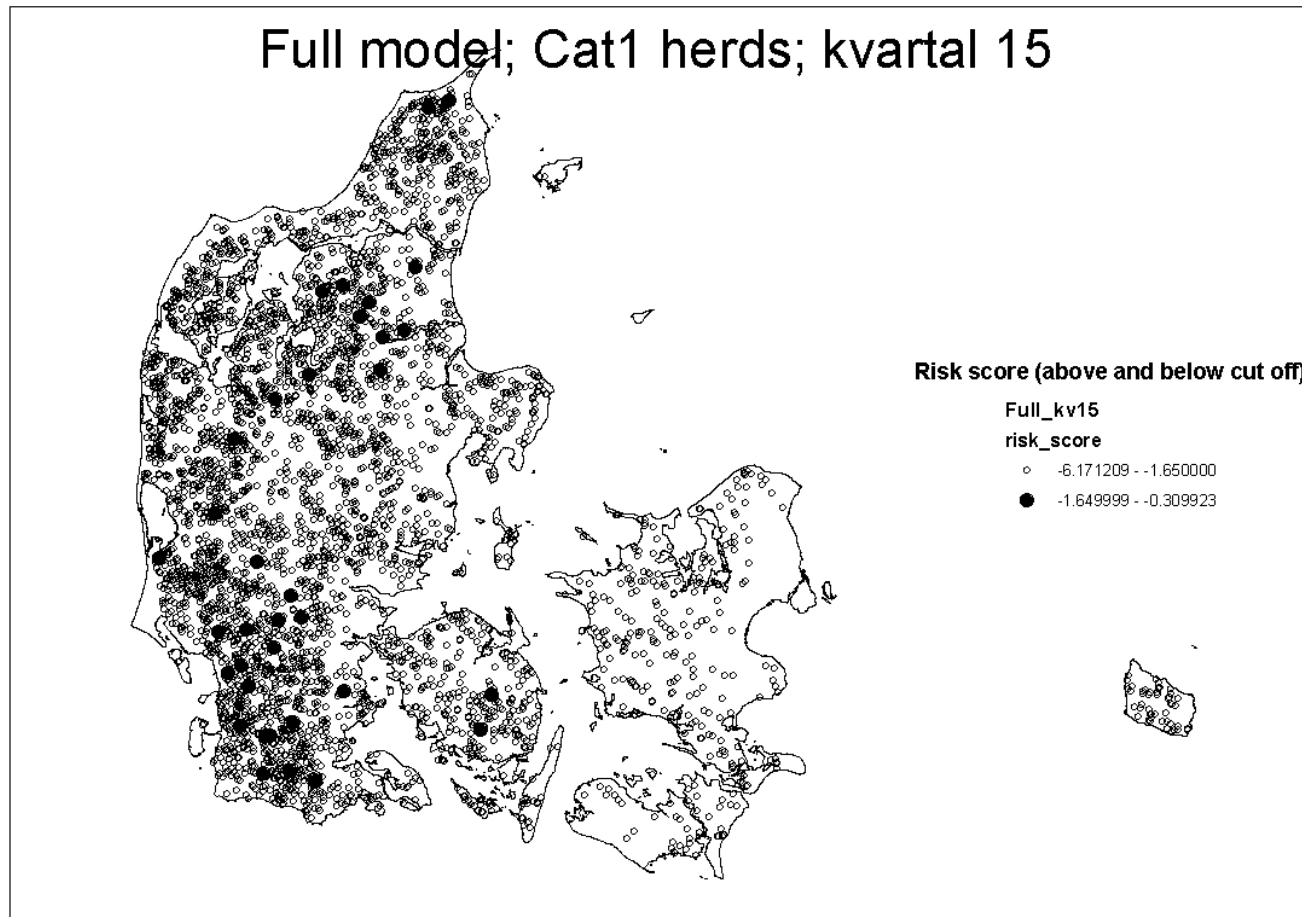
$R_0[\text{Price}[3 \text{ months in Status } 2]$   
 $+\text{cost}(\text{human infections}) \text{ per herd}]$

where  $R_0$  denotes the average excess number of infected herds due to delayed identification.

Higher  $\alpha$  and lower threshold  $r$ .

*These cost values are not known and dependent on legislation*

# Geographical distribution of risk herds ( $\alpha=5$ ) 3<sup>rd</sup> quarter 2007.



- We suggest that risk herds may be defined as herds with a risk score over a threshold  $r$ , with  $r$  taking a value from  $-1.05$  and lower, depending on the nature of sanctions and the importance of detecting status changes.
- *Potential uses if risk index: replacement of the current classification system; potential legal conflicts should be clarified.*
- *Alternatively, a mandatory notice to the farmer on a risk herd classification, allowing voluntary interventions;*
- *Coming legislation should encourage farmers to intervene. However, cost to society is higher than the cost to individual farmers due to spread of disease, so a higher  $\alpha$  value and thus lower threshold  $r$  could apply.*

# Acknowledgement

- We thank Jørgen Nielsen from the Danish Cattle Federation for providing register data from the Danish Cattle Database. Thanks Jørgen.